Workshop Materials

Discussion Paper:

"Advancing the Development of Biomarkers in Traumatic Brain Injury"

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The information and questions contained in this document are not binding and do not create or propose new requirements or expectations for affected parties, nor is this document meant to convey FDA's proposed or recommended approaches or guidance. Rather, the information contained in this document offers background and considerations regarding the scientific and regulatory considerations to identify potential biomarkers for traumatic brain injury (TBI) for discussion at FDA's public workshop on March 3, 2016.

I. INTRODUCTION

The FDA is releasing this discussion paper in preparation for the "Advancing the Development of Biomarkers in Traumatic Brain Injury" public workshop, which will be held at FDA's White Oak Campus in Silver Spring, Maryland on March 3rd, 2016.

The agency is hosting this workshop to engage key stakeholders (e.g., clinicians, researchers, manufacturers, armed forces, government agencies, patient advocates and patients) in an open discussion on the scientific and clinical considerations related to identification and regulation of potential biomarkers for TBI. Establishing biomarkers for TBI has the potential to improve our diagnostic capabilities, understand and monitor the pathological processes involved, and target treatment in clinical trials to support development and approval of medical products. This workshop seeks to address the evidentiary gaps and challenges associated with biomarker development in order for their utilization to increase the innovation of medical products for TBI. The FDA will use the information and feedback from this workshop to develop a strategy that will promote advances in this rapidly evolving area.

This discussion paper provides background information and questions for workshop attendees to consider in advance and will help facilitate discussion. While the scientific and clinical considerations for biomarkers in TBI provided represent FDA's focus, we look forward to hearing other considerations and questions at the workshop.

II. BACKGROUND

A. TBI and the critical need for biomarkers in the management of TBI

TBI remains a major public health problem in our society, and it is a contributing factor in a third of all injury-related US deaths. According to the US Center for Disease Control and Prevention (CDC), every year in the US alone, about 2.5 million patients of varying age groups seek medical care for a range of TBI-caused acute and sustained neurological and neuropsychiatric symptoms that are markedly heterogeneous. An estimated 2% of the U.S. population lives with TBI-caused disabilities, and the economic impact of TBI on the nation has been enormous, with an estimated total direct and indirect cost of $77 billion per year.[1,2]

Among TBI, mild TBI (mTBI) is estimated to account for 80–90% and the importance of apparently mild injuries has been recognized as a major public health crisis.[3] The reasons being, first, most mTBI patients make a seemingly complete recovery, and early identification of patients who are likely to develop persistent symptoms or neuropsychological deficits is difficult. Second, because mortality in mTBI is rare, the diagnostic assessments commonly used in more severely injured patients are not sensitive enough to assess the subtle cognitive and behavioral sequalae that often result from mTBI.

[1] http://www.cdc.gov/traumaticbraininjury/index.html
[2] Faul M, Xu L, Wald MM, Coronado VG. Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths 2002–2006. Atlanta (GA): US Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, 2010: 1–71.
[3] Control NCfIPa. Report to Congress on mild traumatic brain injury in the United States: steps to prevent a serious public health problem. Atlanta, GA: Centers for Disease Control and Prevention, 2003.

The growing concerns about the long-term sequelae of mild TBI in civilians, military and sports make this a clinically important topic and there is a greater awareness for the need to find better ways to diagnose, treat, and prevent all forms of TBI, with a strong emphasis on mTBI.

Decades of well-designed clinical trials have failed to demonstrate clinically meaningful outcomes in patients, despite ongoing findings and reports of promising therapies and treatments in experimental animal models.[4] Those animal models often addressed a single spectrum of brain pathology at a focused location, unlike most brain injuries, which are diffuse and heterogeneous in nature. This limited progress stems, in part, from our inability to precisely diagnose this multi-factorial condition, to accurately define patient selection criteria for clinical trials based on injury characteristics, and to reliably measure the effects of treatments over time.

Particularly, diagnosis of TBI in the acute setting remains a major obstacle, as "gold standard" diagnostic criteria for TBI have not yet been established, even with the availability of several published diagnostic criteria. Among them are several diagnostic criteria that are commonly used both clinically and for determining subject eligibility for TBI clinical trials. These include criteria published by Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine [5]which defines a mTBI as a traumatically induced physiologic disruption of brain function, as manifested by one of the following (a) any period of loss of consciousness (LOC), (b) Any loss of memory for events immediately before or after the accident, (c) any alteration in mental state at the time of the accident, and (d) focal neurologic deficits, which may or may not be transient. The additional criteria for defining moderate TBI are (i) length of hospital stay at least 48 hours, (ii) GCS score of 9-12 or higher, (iii) operative intracranial lesion and (iv) abnormal CT scan findings. Other TBI diagnostic criteria have been

[4] http://www.ninds.nih.gov/disorders/tbi/detail_tbi.htm#3218_6
[5] https://www.acrm.org/wp-content/uploads/pdf/TBIDef_English_10-10.pdf

published by the Centers for Disease Control (CDC), various sports medicine organizations, and brain injury associations. There is considerable overlap among the various TBI diagnostic criteria; however, there are also different criteria for diagnosing more severe TBI. More recently, the Diagnostic and Statistical Manual – Version 5 (DSM-5) published by the American Psychiatric Association now include categories of major and minor neurocognitive disorders due to TBI.[6] This requires that a patient meets the general criteria for a major or minor neurocognitive disorder plus evidence of TBI defined as an impact to the head or other mechanisms of rapid movement or displacement of the brain within the skull, with one or more of the following- (a) loss of consciousness, (b) posttraumatic amnesia, (c) disorientation and confusion, (d) Neurological signs (e.g., neuroimaging demonstrating injury; a new onset of seizures, a marked worsening of a preexisting seizure disorder, visual field cuts, anosmia, hemiparesis).

Given the numerous and varied diagnostic criteria for TBI, clinicians and researchers often rely upon the Glasgow Coma Scale (GCS)[7] which is the universal clinical index for head injury severity that classifies TBI as mild, moderate and severe. While the GCS has proved to be useful in the clinical management and prognosis of TBI, it does not provide specific information about the pathophysiologic mechanisms responsible for the neurological deficits. Thus, GCS has major limitations, with poor discrimination that may obscure meaningful differences among diverse subgroups of TBI patients with different prognoses.[8] Another essential tool in the care of TBI patients is neuroradiology and Computed Tomography (CT) scans are the most commonly used to diagnose acute problems which may be life threatening and require emergent treatment such as surgery. Although CT is highly effective in detecting bleeding within and surrounding the brain (hematomas) as well as brain swelling (edema), which may require

[6] http://dsm.psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596
[7] Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974; 2: 81–84.
[8] Saatman KE, Duhaime AC, Bullock R, Maas AI, Valadka A, Manley GT. Classification of traumatic brain injury for targeted therapies. J Neurotrauma. 2008;25:719-738.

emergency surgery, it is much more limited in its ability to detect the widespread microscopic injury to axons that leads to many of the long term problems experienced by TBI patients. It is not unusual for the CT scan to be entirely normal in a patient with TBI particularly patients with milder TBI including concussion. Thus, the current criteria and tools, used for diagnosis and patient selection in TBI clinical trials are insensitive to the more subtle underlying pathology following mTBI and have not been validated as predictive biomarkers or endpoints sufficient to evaluate differential effectiveness of experimental treatments among TBI phenotypes.

Therefore, there is a critical need for identifying, developing and validating biomarkers to enhance the efficiency of clinical trials to evaluate potential of TBI diagnostics and treatments. As a step towards achieving this goal, FDA is engaging various stakeholders to initiate early discussions on the scientific and clinical considerations associated with the analytical and clinical validation of all categories of TBI biomarkers including: (1) susceptibility/risk biomarkers, (2) diagnostic biomarkers, (3) monitoring biomarkers, (4) prognostic biomarkers, (5) predictive biomarkers, (6) pharmacodynamic/response biomarkers, and (7) safety biomarkers.

B. Biomarker Glossary and Definitions

Recently, the FDA-NIH Joint Leadership Council identified the harmonization of terms used in translational science and medical product development as a priority need, with a focus on terms related to study endpoints and biomarkers.[9] Working together with the goals of improving communication, aligning expectations, and improving scientific understanding, the two agencies developed the *BEST* (Biomarkers, EndpointS, and other Tools) Resource.[10] The *BEST* comprises a glossary that aims to capture distinctions between biomarkers and clinical assessments and to describe their distinct roles in

[9] http://www.ncbi.nlm.nih.gov/books/NBK326791/
[10] http://www.ncbi.nlm.nih.gov/books/NBK338448/

biomedical research, medical product development, and clinical practice. NIH and FDA intend to use the definitions included in this glossary when communicating on topics related to its contents (e.g., biomarkers) to ensure a consistent use of the terms and therefore, a common understanding of the issues. The *BEST* glossary is meant to be a "living" resource that will be periodically updated with additional terms and clarifying information. A few key Definitions from BEST glossary include:

Biomarker: A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives.

Context of Use: A statement that fully and clearly describes the way the medical product development tool is to be used and the medical product development-related purpose of the use.

Intended Use: The specific clinical circumstance or purpose for which a medical product or test is being developed. In the regulatory context, "intended use" refers to the objective intent of the persons legally responsible for the labeling of medical products.

C. FDA regulatory pathways to integrate biomarkers in medical product development program

The discovery, validation, regulatory acceptance, qualification, and use of biomarkers adequate for a variety of drug/device development and regulatory decision-making purposes are areas of tremendous interest and need. There are generally two pathways through which biomarkers can be accepted by the FDA for use in medical product development.

(i) Drug or Device Development and Approval Processes:

First, during the drug/device development and approval process, a manufacturer may engage directly with FDA review staff to reach agreement on the use of a particular biomarker in a given drug/device development program. These interactions are critically important if the biomarker is intended to either serve as a surrogate endpoint or be used as a criterion for restricting use in the population. This pathway may be efficient for a single drug/device development. To use a biomarker in the context of medical product development without qualification, sponsors and developers contact the appropriate office or review division for the medical product. For Drug Approval Process- biomarkers can be accepted through IND and NDA submissions and information on how drugs are developed and approved is available on FDA's website.[11] For Device Clearance and Approval Process- biomarker tests can be accepted through premarket submissions and information about premarket submissions of assays, instruments, and other devices used to measure biomarkers is available on FDA's website.[12]

(ii) Biomarker and Biomarker test Qualification:

In the second fairly new mechanism, manufacturers, patient- or disease-specific foundation, health research organization, or consortium may request regulatory "qualification" of a biomarker for a particular context of use through the FDA's Biomarker Qualification Program. This mechanism is advantageous for biomarkers with broader application across therapeutic areas and/or for which disparate data sources must be aggregated (e.g., through consortium efforts) to provide sufficient evidence of biomarker utility.[13] Biomarkers being considered for qualification are conceptually independent of the specific test performing the measurement. A biomarker, however, cannot become qualified without a reliable means to measure it. Therefore the performance characteristics of the

[11] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/default.htm
[12] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/
[13] Amur S, LaVange L2, Zineh I, Buckman-Garner S, Woodcock J. Biomarker Qualification: Toward a Multiple Stakeholder Framework for Biomarker Development, Regulatory Acceptance, and Utilization. Clin Pharmacol Ther. 2015; 98(1):34-46.

test(s) used to provide the biomarker data will be considered. However, FDA clearance of a testing device for marketing does not imply that the biomarker it measures has been demonstrated to have a qualified use in drug development and evaluation. Additionally, qualification of a biomarker does not automatically imply that a specific test device used in the qualification process for a biomarker has been reviewed by FDA and cleared or approved for use in patient care. Information on Drug Development Tool Program[14] and biomarker qualification through Biomarker Qualification Program[15] are available on FDA's website. For biomarker test qualification and use in medical device development, please refer to the Medical Device Development Tools Pilot Program.[16]

FDA intends to increase the transparency of regulatory pathways to sponsors and developers. This workshop supports increasing the awareness of the following pathways. Additional steps include hearing from all stakeholders at this workshop on ways to further facilitate biomarkers reaching the marketplace.

III. WORKSHOP FOCUS

The FDA recognizes the value of supporting the biomarker development in TBI. This workshop aims to examine potential biomarkers, discuss the challenges and solutions related to biomarker development methodologies, and establish strategies for data standardization, sharing and analysis of big data sets for Traumatic Brain Injury (TBI). The following topic areas will be addressed during the workshop, including public discussions of the questions below.

[14] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/
[15] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284076.htm
[16] http://www.fda.gov/MedicalDevices/ScienceandResearch/MedicalDeviceDevelopmentToolsMDDT/

(A) Examine Potential Neurological Injury markers and Emerging Neurological functional impairment markers

Objectives:

1. Identify the potential biomarkers for TBI and describe existing scientific evidence for these biomarkers
2. Identify evidentiary gaps in scientific and clinical knowledge for these TBI biomarkers
3. Describe challenges and solutions in developing tests for these biomarkers in TBI
4. Discuss challenges and solutions in clinical and analytical validation of the associated tests for biomarkers of TBI
5. Considerations for statistical analyses of biomarker data

Questions for consideration:

a. What measures are currently used for screening, diagnosis, and monitoring of TBI? What is the strength of scientific and clinical evidence supporting these measures?

b. How does the lack of accepted "gold standard" clinical diagnostic criteria for the spectrum of TBI limit our ability to identify biomarkers and develop tests? How should candidate TBI biomarkers be evaluated to determine clinical utility and benefit? Are there current efforts to improve upon and reach consensus on diagnostic criteria in TBI? If so, what are current barriers and solutions to improving clinical diagnostic criteria for TBI?

c. What current or perceived barriers to conducting successful clinical trials in TBI would be addressed by regulatory qualification of biomarkers and associated tests in TBI?

d. There is a need for screening following the injury that can be obtained outside of a clinical environment. For example, evaluation of a football player on the field sideline to determine the reaction time and quantitate the assessment of injury. What benefits and risks are associated with these device-based assessment methods and how would these be validated?

e. Looking at the horizon of new therapeutic development, what biomarker related considerations would potentially increase the probability of success? What NIH and other government funding opportunities are available?

f. To integrate biomarkers into medical product development, what should be considered when deciding whether biomarker qualification is the appropriate pathway? What categories of biomarkers can be qualified through Biomarker Qualification Program?

g. Validation (analytical and clinical) is an important part of clinical and regulatory acceptance of biomarker tests for TBI. What are expectations for analytical validation of candidate biomarker tests in TBI prior to use in clinical trials? Clinical practice? What types of evidence should be used to clinically validate newly proposed biomarker tests for TBI?

(B) Strategies for improving data standardization, sharing, and application of big data analytics for more efficient data integration and evidence synthesis in biomarker development.

Every patient generates a large and diverse amount of digital data in the form of clinical notes, images, sensor and genomics data, and various lab results. With the decreasing costs of data storage, it is now possible to create massive repositories of such data from a large number of patients. This creates the opportunity to take advantage of big data analytics methods and harness the useful information hidden in the data in order to improve patient care. With the opportunity of big data resources, also comes the

challenge of integrating and understanding the relationship and integration of complex data sets. In particular, the complex nature of TBI poses diagnostic and therapeutic challenges that make it a good candidate for application of big data methods. Large volumes of data are required in TBI research in order to build sophisticated statistical models or artificial intelligence systems, and to discover trends and correlations in longitudinal records. In addition, big data methods provide the opportunity for fusion and integration of preclinical, clinical, and epidemiological data, and thereby enable more comprehensive evidence synthesis and facilitate TBI biomarker development, from discovery to regulatory approval and clinical implementation.

While the potential applications and benefits of using big data analytics in TBI biomarker research are numerous and diverse, there are several challenges that need to be addressed for these methods to be applicable and successful. The challenges and areas of interest include (but are not limited to) the following:

- Need for strategies to address data standardization, harmonization, taxonomy and ontology
- Collection and aggregation of various data types from heterogeneous sources
- Creation of infrastructures that allow for secure data access and sharing, while preserving data ownership, integrity, and confidentiality. Additionally, such repositories should provide the end users with proper database access and query methods (e.g. support for SQL queries), detailed documentation, and capability to integrate multiple sources of data (i.e. preclinical, clinical, and epidemiological).
- Development of new scalable analytic and visualization tools applicable to large volumes of structured and unstructured data

- Development of analysis methods that can deal with biomarker-specific challenges (e.g., multidimensionality of per subject data relative to scarcity of study subjects)

Objectives:

1. Explore existing and potential big (clinical and non-clinical) datasets and patient registries pertaining to TBI (TED Metadataset, NINDS CDE, FITBIR, etc.)

2. Identify key areas where big data can be used in discovery or validation of TBI biomarkers, as well as in improving patient outcomes, and designing more successful clinical trials

3. Explore hardware platforms, software, and analytic tools that can be used for big data applications

4. Identify barriers to data aggregation, dissemination, and application, and discuss strategies to address these barriers.

Questions for consideration:

a. Existence of multiple data collection and storage sources present challenges in data integration and application of big data analytics for TBI. What are the specific challenges? How can consortia, registries, funding agencies and other collaborative groups reinforce a culture of data sharing to maximize the overall utility of big data sets? How can these data be harmonized and aggregated?

b. How can big data analytics help solve challenges in TBI research (For example: automatic detection and quantification of TBI lesions in neuroimaging for diagnosis, discovery of

biomarkers for TBI, fusion of multiple patient data sources, outcome prediction, and impact on selection and stratification of patients in clinical trials)?

c. When dealing with multi-variate data, how large a dataset is needed for estimating the variables depends on the number of variables. Since a large number of variables are expected to be involved for TBI, it will require a large quantity of patient data. What are the gaps and possibilities for addressing this issue?

d. What are existing non-TBI examples of discoveries that were made using big data? What lessons learned from these examples can be applied to TBI?

IV. SUBMITTING PUBLIC COMMENTS

Regardless of attendance at the public workshop, if you have information related to this workshop that you wish the FDA to consider, please post your material to Docket Number FDA-2016-N-0343 at http://www.regulations.gov. Instructions for posting material can be found at: http://www.fda.gov/RegulatoryInformation/Dockets/Comments/ucm089193.htm or in writing to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852 (Docket ID: FDA-2016-N-0343). Both individuals and groups may submit materials. Please note that the docket will be public, and not appropriate for addressing individual confidential medical device concerns.

V. APPENDIX A: A Backgrounder on Medical Device Regulation

For general information on how to market a medical device please refer to the following FDA website: http://www.fda.gov/training/cdrhlearn/default.htm. This is a link to the CDRH web page for multimedia industry education that includes learning modules describing many aspects of medical device and

radiation emitting product regulations, covering both premarket and post market topics. Additional resources are provided as follows:

A. Medical Device Classification

There are three classes of devices: Class I (general controls), Class II (special controls), and Class III (premarket approval), with the level of regulatory control increasing from Class I to Class III based on the types of regulatory controls considered necessary to provide reasonable assurance of safety and effectiveness.[17] For more information on device classification please refer to the following FDA website:http://www.fda.gov/medicaldevices/deviceregulationandguidance/overview/classifyyourdevice/default.htm

B. Marketing Applications

Information on the various types of marketing applications can be found on the following FDA websites:

Premarket Notification (510(k)):

http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/premarketnotification510k/default.htm

Evaluation of Automatic Class III Designation (De Novo Classification Process):

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM273903.pdf

C. Investigational Device Exemptions (IDEs)

[17] *21 Code of Federal Regulations (CFR) 860.3(c)*

Section 520(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)[18] establishes a framework for FDA to study medical devices for investigational use. This provides an exemption from certain requirements so that experts qualified by scientific training and experience can investigate their devices' safety and effectiveness. This exemption is known as IDE. In order to study a significant risk device in human subjects, a sponsor (defined here as the person responsible for initiating the investigation) must receive approval of an IDE application prior to beginning the investigation.[19]

D. Medical Device Master Files (MAFs)

Often a sponsor submitting a premarket submission (i.e., an applicant) needs to use another party's product (e.g., ingredient, subassembly, or accessory) or facility in the manufacture of the device. In order that a sound scientific evaluation may be made of the premarket medical device submission, the review of data and other information related to the other party's product, facility, or manufacturing procedures is required. The other party, while willing to allow FDA's confidential review of this information, may not want the applicant to have direct access to the information. To help preserve the trade secrets of the ancillary medical device industry and at the same time facilitate the sound scientific evaluation of medical devices, FDA established the device master file system. Please refer to the following FDA webpage for additional information on device master files: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm142714.htm

[18] *21 U.S.C. § 360j(g)*

[19] *21 CFR 812.20*

VI. APPENDIX B: Glossary of Acronyms and Abbreviations

510(k): Premarket Notification

BEST: Biomarkers, EndpointS, and other Tools

BQP: Biomarker Qualification Program

CDC: Center for Disease Control and Prevention

CDE: Common Data Elements

CDER: Center for Drug Evaluation and Research

CDRH: Center for Devices and Radiological Health

CT: Computed Tomography

DDT: Drug Development Tool

FDA: U.S. Food and Drug Administration

FITBIR: Federal Interagency Traumatic Brain Injury Research

FNIH: Foundation for the National Institutes of Health

GCS: Glasgow Coma Scale

IDE: Investigational Device Exemption

IND: Investigational New Drug

LOC: Loss of Consciousness

MAF: Medical Device Master Files

MDDT: Medical Device Development Tool

mTBI: Mild Traumatic Brain Injury

NDA: New Drug Application

NIH: National Institutes of Health

NINDS: National Institute of Neurological Disorders and Stroke

PMA: Premarket Approval

TBI: Traumatic Brain Injury

TED: Traumatic Brain Injury Endpoints Development